(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 April 2003 (24.04.2003)

PCT

(10) International Publication Number
WO 03/033593 A1

(51) International Patent Classification[7]: C08L 67/04, C08G 63/08, A61K 9/10, 47/34

(21) International Application Number: PCT/KR02/01943

(22) International Filing Date: 17 October 2002 (17.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2001/64164 18 October 2001 (18.10.2001) KR

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: PH RESPONSIVE BIODEGRADABLE POLYLACTIC ACID DERIVATIVES FORMING POLYMERIC MICELLES AND USES THEREOF FOR POORLY WATER SOLUBLE DRUG DELIVERY

(57) Abstract: Polylactic acid derivatives capable of forming micelles in an aqueous solution with a pH of 4 or above, having one terminal carboxyl group. The polylactic acid derivatives may be applied as a drug delivery system in various forms since poorly water soluble drugs can be entrapped inside the micelles.

CLAIMS

We claim:

1. A polylactic acid derivative capable of forming micelles in an aqueous solution with a pH of 4 or more, said polylactic acid derivative can be represented by formula (I):

$$RO\text{-}CHZ\text{-}[A]_n\text{-}[B]_m\text{-}COOM \qquad (I)$$

wherein A is –COO-CHZ; B is –COO-CHY-, -COO-$CH_2CH_2CH_2CH_2CH_2$-, or –COO-$CH_2CH_2OCH_2$-; R is hydrogen, an acetyl, benzoyl, decanoyl, palmitoyl, methyl, or ethyl group; Z and Y are hydrogen, methyl, or phenyl groups; M is hydrogen, sodium, potassium, or lithium; n is an integer from 1 to 30; and m is an integer from 0 to 20.

2. The polylactic acid derivative according to claim 1 wherein the number average molecular weight of the polylactic acid derivative is 500 to 2,000 Daltons.

3. The polylactic acid derivative according to claim 1 wherein the polylactic acid derivative is a member selected from the group consisting of D,L-polylactic acid, a copolymer of D,L-lactic acid and mandelic acid, a copolymer of D,L-lactic acid and glycolic acid, a copolymer of D,L-lactic acid and caprolactone, and a copolymer of D,L-lactic acid and 1,4-dioxane-2-one.

4. The polylactic acid derivative according to claim 1 wherein M is sodium, potassium, or lithium.

5. The polylactic acid derivative according to claim 1 wherein R is decanoyl or palmitoyl.

6. A polylactic acid derivative, made from a process comprising:

1) polycondensing monomers of a polylactic acid derivative at an elevated temperature under a reduced pressure;

2) adding distilled water to the product of step 1 to precipitate the polylactic acid

derivative and thereby removing a low-molecular weight oligomer;

3) adding the polylactic acid derivative to a neutral or alkaline aqueous solution to dissolve the polylactic acid derivative;

4) isolating the polylactic acid derivative from the solution of step 3; and

5) adding an alkali metal salt to the polylactic acid derivative obtained in step 4.

7. The polylactic acid derivative according to claim 6 wherein the reaction temperature of the polycondensation in step 1 is 100 to 200℃.

8. The polylactic acid derivative according to claim 6 wherein the polycondensation in step 1 is conducted under a pressure of 25 to 0.1 mmHg.

9. The polylactic acid derivative according to claim 6 wherein isolating the polylactic acid derivatives in step 4 is conducted by adding acid to the aqueous solution of step 3 and adjusting pH to 1.5 ~ 2.5 to precipitate the polylactic acid derivatives.

10. The polylactic acid derivative according to claim 6 wherein isolation of the polylactic acid derivative in step 4 is conducted by adding an organic solvent to the aqueous solution of step 3 to extract the polylactic acid derivative.

11. The polylactic acid derivative according to claim 6 wherein the alkali metal salt in step 5 is selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate and lithium carbonate.

12. A polylactic acid derivative of formula (I) wherein R is an acetyl, benzoyl, decanoyl, palmitoyl, methyl, or ethyl group, prepared from a process comprising the steps of:

1) polycondensing a monomer of a polylactic acid derivative at an elevated temperature and under a reduced pressure;

2) adding distilled water to the product of step 1 to a precipitate a polylactic acid derivative and thereby removing low-molecular weight oligomers;

3) adding the polylactic acid derivative to a neutral or alkaline aqueous solution to dissolve the polylactic acid derivative;

4) isolating the polylactic acid derivative from the solution of step 3;

5) reacting the polylactic acid derivative obtained in step 4 with acetic anhydride, acetyl chloride, benzoyl chloride, decanoyl chloride, palmitoyl chloride, methyl iodide, or ethyl iodide to substitute the hydroxyl terminal group; and

6) adding an alkali metal salt to the substituted polylactic acid derivatives.

13. The polylactic acid derivative according to the claim 12 wherein the reaction temperature of the polycondensation in step 1 is 100 to 200°C.

14. The polylactic acid derivative according to the claim 12 wherein the polycondensation in step 1 is conducted under a pressure of 25 to 0.1 mmHg.

15. The polylactic acid derivative according to the claim 12 wherein the step of isolating the polylactic acid derivative in step 4 is conducted by adding acid to the aqueous solution of step 3 and adjusting pH to 1.5 ~ 2.5 to precipitate the polylactic acid derivative.

16. The polylactic acid derivative according to the claim 12 wherein the step of isolating the polylactic acid derivative in step 4 is conducted by adding an organic solvent to the aqueous solution of step 3 to extract the polylactic acid derivative.

17. The polylactic acid derivative according to the claim 12 wherein the alkali metal salt in step 5 is selected from the group consisting of sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, and lithium carbonate.

18. A polymeric composition containing the polymeric micelles comprising the polylactic acid derivative according to any one of the claims 1 to 17.

19. A pharmaceutical composition wherein a poorly water soluble drug is entrapped in the polymeric micelles comprising the polylactic acid derivative according to any one of the claims 1 to 17.